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T. HELEN PAYNE
AVENTIS PASTEUR, INC. INTELLECTUAL PROPERTY
ONE DISCOVERY DRIVE
SWIFTWATER, PA 18370

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,638	RYALL, ROBERT P.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-33* is/are rejected.

7)☒ Claim(s) *18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1120, 1105*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

Applicant's Amendment

1) Acknowledgment is made of Applicant's amendment filed 10/14/03 in response to the non-final Office Action mailed 04/15/03.

Status of Claims

2) Claims 1-17 have been canceled via the amendment filed 10/14/03.

New claims 18-33 have been added via the amendment filed 10/14/03.

Claims 18-33 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Information Disclosure Statements

5) Acknowledgment is made of Applicants' Information Disclosure Statements filed 11/05/03 and 11/20/03. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Objection(s) Moot

6) The rejection to claims 1, 2 and 16 made in paragraph 12 of the Office Action mailed 04/15/03 is moot n light of Applicant's cancellation of the claims.

Rejection(s) Moot

7) The rejection of claims 1 and 10, and claims dependent therefrom, made in paragraph 4 of the Office Action mailed 04/15/03 under 35 U.S.C. § 101 as being directed to a non-statutory subject matter, is moot in light of Applicant's cancellation of the claims.

8) The rejection of claims 1-8 and 10-16 made in paragraph 5 of the Office Action mailed 04/15/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicant's cancellation of the claims.

9) The rejection of claims 1-3, 5-7, 10, 11 and 13-15 made in paragraph 7 of the Office Action mailed 04/15/03 under 35 U.S.C. § 102(b) as being anticipated by Costantino *et al.* (*Vaccine* 10: 691-698, 1992), Lieberman *et al.* (*JAMA* 275: 1499-1503, 1996), or Twumasi *et al.* (*J. Infect. Dis.* 171: 632-638, 1995), is moot in light of Applicant's cancellation of the claims.

10) The rejection of claims 1-3, 5-7, 10, 11 and 13-15 made in paragraph 8 of the Office Action mailed 04/15/03 under 35 U.S.C. § 102(b) as being anticipated by Granoff (WO 98/58670), is moot in light of Applicant's cancellation of the claims.

11) The rejection of claims 1, 6, 8, 10, 14 and 16 made in paragraph 10 of the Office Action mailed 04/15/03 under 35 U.S.C. § 103(a) as being unpatentable over Granoff (WO 98/58670), is moot in light of Applicant's cancellation of the claims.

12) The rejection of claims 1, 4, 10 and 12 made in paragraph 11 of the Office Action mailed 04/15/03 under 35 U.S.C. § 103(a) as being unpatentable over Granoff (WO 98/58670), is moot in light of Applicant's cancellation of the claims.

New Rejection(s)

Applicant is asked to note the new rejection(s) made in this Office Action. Applicant's amendments i.e., submission of new claims, necessitated the new ground(s) of rejection presented in this Office Action.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

13) Claims 22-32 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 22 includes limitations such as: 'two distinct protein-polysaccharide conjugates, wherein the first conjugate comprises a purified capsular polysaccharide of serogroup W-135 and a second conjugate comprises a purified capsular polysaccharide selected from the group consisting of serogroup Y, A or C'. Claims 23-28 include specific bivalent combinations. New claim 29 includes limitations such as: 'three distinct protein-polysaccharide conjugates, wherein a first conjugate comprises a purified capsular polysaccharide of serogroup W-135 and a second conjugate comprises a purified capsular polysaccharide selected from the group consisting of serogroup Y, A or C and a

third conjugate comprising a purified capsular polysaccharide selected from the group consisting of Y, A and C, wherein the second conjugate is different from the third conjugate'. Claims 30-32 include specific trivalent conjugate combinations. However, except for the tetravalent meningococcal ACW-135Y conjugate combination and the A-C bivalent conjugate combination, there is no descriptive support in the specification, as originally filed for the specifically claimed bivalent and trivalent immunogenic composition embodiments comprising the specific serogroup capsular polysaccharides. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or invited to point to specific pages and line numbers in the originally filed specification where support for such recitations can be found.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

14) Claims 18-33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claim 18 is incorrect and/or confusing in the recitation: 'one or more a carrier protein(s)'.

(b) Claim 18 is vague and indefinite in the recitation: "derived", because it is unclear what is encompassed in this recitation. Does the process of "deriving" encompass: extraction, isolation, separation, purification, recombinant production, modification or expression on cell surface?

(c) Claims 19-29 and 33 are indefinite and/or lack proper antecedence in the recitation 'at least one of the capsular polysaccharide is from serogroup .....' without distinctly pointing out the serogroup is of *--Neisseria meningitidis--*.

(d) In claim 29, for clarity and consistency with the recitation used in line 2 of the claim, it is suggested that Applicants replace the limitation 'comprising' in lines 3 and 5 of the claim with the limitation --comprises--.

(e) Claims 30-32 are indefinite and meaningless in the recitation 'comprises Y', 'comprises A' and 'comprises C' respectively. What does Y, A or C stand for.

(f) Claims 19-33 which depend directly or indirectly from claim 18 are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. 102

15) Claims 18-33 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chong *et al.* (WO 99/42130).

Chong *et al.* disclosed a multivalent immunogenic molecule comprising multiple purified capsular polysaccharides or oligosaccharides (i.e., depolymerized polysaccharides) of *Neisseria meningitidis* derived from serogroup A, C, W-135 and Y, each linked to a carrier protein for use as a medicament against meningitis (see claims 1, 6-8, 39 and 40; paragraph bridging pages 9 and 10; pages 10 and 12; and Examples 1, 2 and 4).

Claims 18-33 are anticipated by Chong *et al.*

Rejection(s) under 35 U.S.C. 103

16) Claims 18-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Granoff (WO 98/58670 - already of record) ('670) or Ambrosch *et al.* (*Bull WHO* 61 (2): 317-323, 1983) in view of Andre *et al.* (*In*: *Modern Vaccinology*. (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994), and Levine *et al.* (*In*: *Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997).

Granoff ('670) disclosed a U.S.-licensed quadravalent or tetravalent meningococcal Menomune® polysaccharide vaccine (i.e., immunological composition) comprising immunologically effective amounts of serogroups A, C, Y and W135 meningococcal capsular polysaccharides (see page 18; second paragraph on page 6; and first paragraph on page 20). Granoff ('670) disclosed a meningococcal A, C, Y and W135 polysaccharide-based vaccine wherein the polysaccharides are not conjugated to a carrier protein (see page 6, second full paragraph; last paragraph on page 18; and first paragraph on page 20). Granoff ('670) disclosed a method of conjugating more than one distinct meningococcal capsular polysaccharides to an appropriate carrier molecule, such as, the non-toxic diphtheria toxin mutant, CRM_{197}, to produce a polyvalent or multivalent meningococcal conjugate vaccine (see page 11, second paragraph; and first half of page 12). Granoff ('670) taught

the art-known meningococcal A and C oligosaccharide-based glycoconjugate vaccine, or the trivalent meningococcal A, B and C oligosaccharide-based glycoconjugate (see last paragraph on page 12). Granoff's polyvalent meningococcal conjugate vaccine is contained in aluminum hydroxide adjuvant (see page 19; and Figure 1).

Ambrosch *et al.* taught an immunogenic tetravalent meningococcal polysaccharide vaccine comprising purified serogroup A, C, Y and W 135 capsular polysaccharides. The vaccine is immunogenic in humans (see abstract; Materials and Methods; and Results).

The teachings of Granoff ('670) or Ambrosch *et al.* are explained above, which do not expressly disclose that A, C, Y and W135 meningococcal capsular polysaccharides in their multivalent meningococcal vaccine are conjugated to one or more carrier proteins.

However, Granoff expressly taught the disadvantages of meningococcal polysaccharide vaccines, including the tetravalent A, C, Y and W135 meningococcal Menomune® polysaccharide vaccine, in the statement that: a) they are poorly immunogenic in infants less than 2 years of age, the age group at greatest risk of developing meningococcal disease; b) they do not provide long-lasting protection in older children and adults; and that they induce immunological paralysis of toddlers and adults to meningococcal polysaccharides; and c) they induce immunologic tolerance in infants less than 6 months of age (see the first half of page 3; last half of page 9; and lines 4-10 of page 10). Granoff explicitly taught that anti-meningococcal conjugate vaccines are more effective than unconjugated polysaccharide vaccines in infants and toddlers (see lines 1-4 on page 4). Granoff taught his unexpected discovery that an anti-meningococcal conjugate vaccine composition in adults, as opposed to an unconjugated anti-meningococcal polysaccharide vaccine, induces polysaccharide-responsive memory B cells, long-term immunologic memory and a readily boostable response in vaccinated subjects, both of which factors contribute to more robust and durable protection against meningococcal disease (see first full paragraph on page 9).

Andre *et al.* taught that serotypes B, C, A, Y and W-135 are the most virulent and prevalent *N. meningitidis*. Andre *et al.* also taught that a quadrivalent meningococcal vaccine comprising meningococcal serotypes B, C, Y and W-135 polysaccharides already exists which is immunogenic in children and adults, but very poorly immunogenic in children less than 2 years old, at an age when a vaccine would be most effective. Andre *et al.* further expressly suggested that conjugate vaccines

could be the answer to this problem. See first paragraph on page 45 of Andre *et al.* Andre *et al.* also taught that the first developed group A and C meningococcal vaccines as well as the later developed Y and W-135 meningococcal vaccines though immunogenic in children and adults, are poorly immunogenic in children less than 2 years old, and that conjugate vaccines could be the answer to this problem. See first paragraph on page 45 of Andre *et al.*

Levine *et al.* analyzed the cost-effectiveness of routine infant immunization with a quadrivalent meningococcal polysaccharide, A, C, Y and W-135-protein conjugate vaccine in the United States and concluded that such an immunization with the quadrivalent meningococcal polysaccharide, A, C, Y and W-135-protein conjugate vaccine is likely to have a substantial impact on endemic meningococcal disease and may provide herd immunity (see pages 228-230, especially paragraph bridging pages 229 and 230). Levine *et al.* expressly called on vaccine manufacturers to provide such a conjugate vaccine that is cost-effective (see paragraph bridging pages 229 and 230).

Given the art-recognized disadvantages of the U.S.-licensed quadravalent or tetravalent meningococcal Menomune® polysaccharide vaccine comprising serogroup A, C, Y and W135 meningococcal capsular polysaccharides as taught by Granoff ('670), including their poor immunogenicity in children less than 2 years of age as also taught by Ambrosch *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate the individual serogroup A, C, Y and W135 meningococcal capsular polysaccharides present in the Menomune® polysaccharide vaccine disclosed by Granoff ('670) to the art-known protein carrier, non-toxic diphtheria toxin mutant, CRM_{197}, using art-known conjugation technology to produce the instant invention with a reasonable expectation of success, because Andre *et al.* expressly suggested conjugate vaccines as the answer to the problem poor immunogenicity, and Levine *et al.* expressly taught that routine infant immunization with a quadrivalent meningococcal polysaccharide A, C, Y and W-135-protein conjugate vaccine is likely to have a substantial impact on endemic meningococcal disease and may provide herd immunity. Given Levine's express call for vaccine manufacturers to provide a meningococcal A, C, Y and W-135-protein conjugate vaccine that is cost-effective, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of: a) rendering Granoff's tetravalent meningococcal Menomune® unconjugated polysaccharide vaccine advantageously more effective in infants and toddlers who are

at greatest risk of developing meningococcal disease, and rendering it capable of inducing polysaccharide-responsive memory B cells, long-term immunologic memory, a readily boostable response in vaccinated subjects, and a more robust and durable protection against meningococcal disease as expressly taught by Granoff ('670); b) avoiding the undesirable immunological paralysis of toddlers and adults to meningococcal polysaccharides and avoiding immunologic tolerance in infants less than 6 months of age as expressly taught by Granoff ('670); c) to provide a quadrivalent meningococcal polysaccharide A, C, Y and W-135-protein conjugate vaccine that is likely to have a substantial impact on endemic meningococcal disease and that may provide herd immunity as expressly taught by Levine *et al.*

Claims 18-33 are *prima facie* obvious over the prior art of record.

Objection(s)

17) Claim 18 is objected to for the recitation "N. meningitidis" without italicizing the limitation. To be consistent with the practice in the art, it is suggested that Applicant replace the recitation with *--Neisseria meningitidis--*.

Remarks

18) Claims 18-33 stand rejected.

19) Applicant's amendments necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official

Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347 until January 2004 and (571) 272-0854 beginning February 2004. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER